Depth Profiling of Drug Eluting Stent Coatings with Cluster SIMS

NIST is developing a Secondary Ion Mass Spectrometric (SIMS) method employing an SF_5^+ polyatomic primary ion source for sputtering and Bi_3^+ primary ion to provide a depth profile through drug eluting stent coatings (DES). DES is a new technology that is under development for the treatment of coronary artery disease.

C. Mahoney, A. Fahey (Div. 837) and A. Belu (Medtronic, Inc)

Much excitement has been generated in the cardiology community about drug eluting stents (DES), a promising new treatment for coronary artery disease. A coronary stent is a small coiled wire-mesh tube that is inserted into a blood vessel and expanded using a small balloon during an angioplasty procedure. When the balloon is inflated, the stent expands, locks in place and forms a scaffold to hold the artery open, improving blood flow to the heart muscle and decreasing the probability of restenosis or renarrowing of the artery. These stents often incorporate a drug delivery system consisting of a polymeric layer or coating containing a drug, where the drug acts to further prevent the build up of smooth muscle cells on the stent. It is particularly important in DES to characterize the molecular composition of the surface and near surface region of the device (1-500 nm) because this region controls the biocompatibility and influences the magnitude and temporal variation of drug release.

Secondary Ion Mass Spectrometry (SIMS) has already proven to be a useful tool in the surface analysis of various drug delivery systems. With SIMS, the molecular distribution of both drugs and excipients within a drug delivery systems can be determined with a high degree of spatial resolution (<1µm) and sensitivity (as low as ppm (µg/g)) when compared to other analytical methods such as Raman and IR spectroscopies.

With the advent of polyatomic primary ion sources (C_{60}^+, Bi_3^+ and SF_5^+), which yield significant improvements in molecular signals (up to 1000 fold increase), and result in decreased beam-induced damage accumulation, it is now possible to obtain 3-dimensional compositional information from model systems, particularly at low temperatures which yield optimum results.

The NIST team used Secondary Ion Mass Spectrometry (SIMS) employing an SF_5^+ polyatomic primary ion source for sputtering and Bi_3^+ primary ions for analysis to depth profile through DES coatings obtained from a commercial manufacturer, Medtronic. The images obtained represent the first demonstration of successful 3-D SIMS imaging in real world drug delivery devices.

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Figure 1 (on next page) shows the resulting depth profiles of PLGA/Rapamycin films which were prepared by casting solutions of 2% w/v poly(lactic-co-glycolic acid) (PLGA) containing 5% w/w rapamycin (~6 µm) onto steel substrates. Figure 1a, shows the resulting depth profile acquired at room temperature. As can be seen, the signal starts to decay at SF_5^+ primary ion doses of ~1.3 x 10^{15} SF_5^+ ions/cm^2 and the steel substrate is never reached. However, Figure 1b shows that the depth profile stability is dramatically improved at low temperatures (-100 ^{o}C), as indicated by the relatively constant signal up through SF_5^+ primary ion doses of ~1.5 x 10^{16} SF_5^+ ions/cm^2. At this dose the secondary ions characteristic of the DES coating start to decrease while the corresponding steel substrate intensities increase, indicating that the entire film has been eroded. This result shows that using low temperatures can extend the utility of SF_5^+ to characterize thicker polymeric materials (6.0 µm as opposed to 0.2 µm).

Cluster SIMS at low temperatures has also be used to elucidate the 3-dimensional structure in these DES coatings, as illustrated in Figure 2, which shows secondary ion image overlays of m/z = 99 (fragment characteristic of PLGA) and m/z = 84 (fragment characteristic of Rapamycin) in a PLGA film containing 25% rapamycin. These images were acquired as a function of increasing sputter time or depth, and thus give detailed information on the heterogeneity in the surface and near surface region in these systems as compared to the bulk.

Future Plans: We intend to continue our collaborative work with Medtronic and study the 3-D structure in their Drug Eluting Stents as a function of dissolution time in a phosphate buffered saline.

Related Publications:
Mahoney, C.M.; Patwardhan, D.V.; McDermott, M.K. *Applied Surface Science*. 2006, 19, 6554-6557.

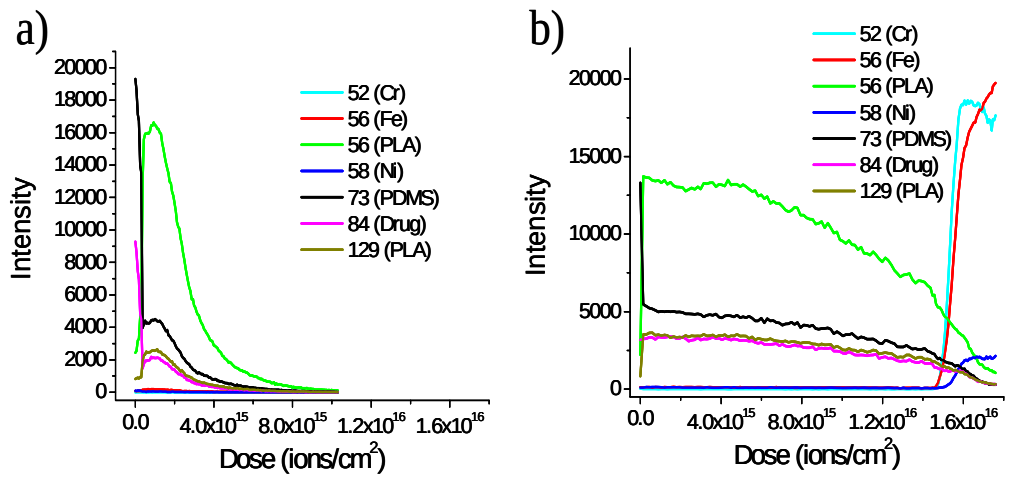

Figure 1. Secondary ion intensities plotted as a function of increasing SF_5^+ dose (directly related to depth into film) for a sample of PLGA containing 5 % (w/w) Rapamycin (~6 µm) coated on steel.
Profiles were acquired at: a) 25 °C, and b) -100 °C

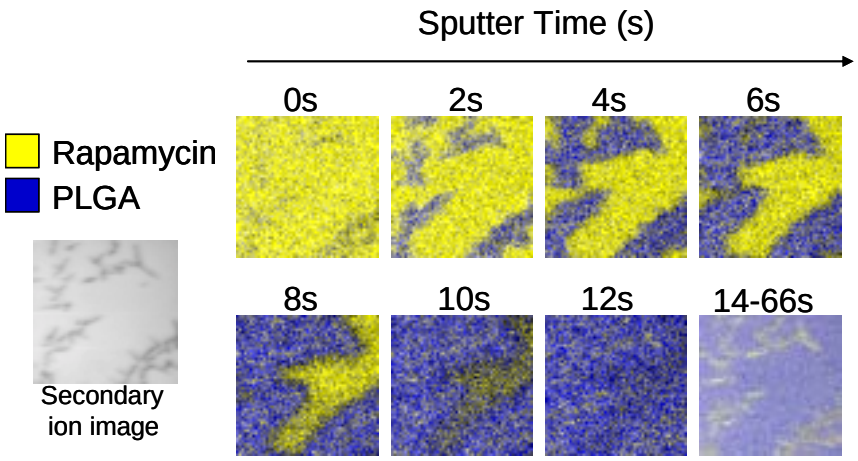

Figure 2. Overlay of Secondary ion images acquired as a function of increasing SF_5^+ sputter time (depth) in a PLGA film containing 25% w/w Rapamycin. Blue represents m/z = 99 (PLGA) and yellow represents m/z = 84 (Rapamycin). These images were acquired with a Bi_3^+ cluster primary ion source.